REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-22 remain pending in the application subsequent to entry of this Amendment.

It is counsel's understanding that the claims examined in the current Action are those contained in the Preliminary Amendment of February 2, 2006.

Claim 10 has been amended for purposes of clarity as discussed in the remarks that follow.

Applicants' Contribution to the Art

It is important to appreciate, as background to the present invention, that this invention relates to the incorporation of active agents into particles of dispersed amphiphile in bulk solvent. The formation of such lipid dispersions, both in lamellar and non-lamellar form, is well known and has been both proposed and applied in the delivery of pharmaceutical agents. Key criteria as to how useful a lipid dispersion system will be for the delivery of such active agents include the level of active agent which can be incorporated into the particles, the stability of that active agent once incorporated and the stability of the (active agent containing) particles in terms of their size distribution and phase behavior.

Different methods for loading active agents into dispersed lipid particles have been proposed for different active agents, but one of the most useful is to suspend the particles in the solution of the required active agent at room temperature, or 37 °C. As indicated in the last paragraph of page 5 of the application as filed, this incubation method provides an "equilibrium" level of loading which has previously been assumed to be the greatest quantity of active agent that could stably be incorporated into amphiphilic particles.

The present inventors have now established that amphiphilic particles may be prepared and subsequently loaded with active agents to a very high level, with a high degree of stability, by forming lipid particles and heating these to an elevated temperature when dispersed in a solution of the active agent. The formation of 9 different compositions of these particles, in the absence of active agents, is described in detail in Example 1 on page 39 and loading by equilibration and by the method of the present invention is described in the subsequent examples for active agents including progesterone, fenofibrate, fulvestrant, ketoconazole, testosterone and octreotide. The loading of these active agents into one or more of nine different amphiphile

compositions has been examined and increases in loading of up to 900 % have been observed in comparison with the prior art method. Furthermore, as indicated in Example 8, the loading of active agents to higher level does not prejudice the stability of the loading or particle size if carried out by the method of the invention.

Response to Prior Art-Based Rejections

The Official Action contains two separate rejections of alleged anticipation. Applicants disagree.

Turning to the specific objections raised in the Office Action, the Examiner believes that the claims of the application are deprived of novelty due to disclosures of US '328 and US '925, both of which were cited in the International Search Report.

To anticipate a claim, a single reference must disclose the claimed invention with sufficient clarity to prove its existence in the prior art. *Motorola Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997). Anticipation rejections are only proper when the "claimed subject matter is identically disclosed or described in 'the prior art,' without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 172 USPQ 524, 526 (CCPA 1972); *see also Akzo N.V. v. International Trade Commission,* 1 USPQ 2d 1241, 1246 (Fed. Cir. 1986); neither of these references meet this high standard and both rejections must be withdrawn.

US '328 relates to the generation of a cream. The generation method disclosed therein provides *the formation* of vesicles by a method of heat treatment. No particles are present prior to this heat-fragmentation method, no active agent is incorporated by that method and no heating in a solution of active agent is disclosed. US '328 therefore discloses a method of fragmentation of a lipid composition but no method for incorporation of an active agent into such a composition.

US '925 relates to a heating method applied in order *to disperse* a non-lamellar phase. There is no heating and cooling step carried out on amphiphile particles since the particles do not exist prior to the heating step. Furthermore, there is no disclosure of heat treatment carried out in a solution of active agents. US '925 thus discloses a method of fragmentation, which might form particles suitable for use in the method of the present invention, but does not disclose that method, nor any particle formed or obtainable thereby.

It is evident that the current claims are novel over the cited documents, for the reasons given above. This novelty was acknowledged by the examiner in the International phase.

Considering next nonobviousness, which the Examiner has not commented upon, as discussed above, the Examples of the present application show that the method recited in claims 1-9 provides an increase in the loading level of active agent into the amphiphile particles of between 20 and 900 %. Evidently, this will have considerable advantages in terms of the quantity of material required to be administered to a patient. Reducing the volume administered in turn decreases pain and swelling and improves patient compliance.

In view of the fact that none of the cited documents provides a method of loading active agents into amphiphilic particles, the problem to be solved by the present application may be defined as providing a method for incorporation of active agents into amphiphile particles, wherein the active agent is incorporated at high level and the resulting particles are stable in terms of loading and particle size. This is provided by the method of the present claims and that method is in no way taught towards by any of the citations. The claims are thus believed evidently novel and inventive in view of the cited prior art. In particular, the prior art cannot teach an improved method for loading an active agent into amphiphilic particles, since no such method is considered therein.

Claim Clarity/Rejection Under 35 USC §112, Second Paragraph

The Examiner has objected that claim 10 is unclear, and therefore that it's dependent claims are also unclear. This objection relates to the stipulation that the amphiphilic particles of claim 10 comprise at least 130% of the maximum incorporation of equivalent particles not containing any active agent, when incubated at 37 °C in an excess of active agent.

The Examiner is interpreting claim 10 to mean that the amphiphilic particles contain 130% of the active agent content of equivalent particles not containing any active agent. He therefore takes the active agent content of both the claimed particles and the equivalent particles to be zero, because 130% of zero is still zero.

Please again review this claim and note that claim 10 is directed to particles comprising at least one structure forming amphiphile and an active agent, characterised by their higher content of active agent in comparison with amphiphilic particles having the same active agent incorporated by the known "equilibration" method.

If particles comprising at least one structure forming amphipile (but no active agent) are incubated in a solution of excess active agent at 37 °C, a quantifiable amount of active agent is incorporated into these particles. The claimed amphiphilic particles are characterised by the fact that they contain 130 % of this quantifiable amount of active agent, i.e. they contain 30 % more active agent than a particle produced by the known methods.

As an example of the above, if a particle having the structure-forming amphiphile GMO is incubated in a solution of active agent at 37 °C and incorporates 10 mg active agent per g of particle after a long equilibration, then claim 10 would require a loaded particle comprising the same structure-forming amphiphile to contain at least 13 mg of the same active agent. The skilled man would easily be able to determine the loading of a particle achievable at 37 °C, by reference to the teachings of the application and therefore the scope of claim 10 is clearly defined.

In order to progress examination, claim 10 has been amended to specify that the level of the active agent incorporated into the particles is at least 130% of the maximum level obtainable by incubating equivalent particles not containing any active agent in a solution of an excess of the active agent at the relevant temperature. It is believed these adjustments to claim 10 will resolve the examiner's concerns and that this rejection will be withdrawn.

Should the examiner require further information, please contact the undersigned. Reconsideration and allowance are solicited.

Respectfully submitted,

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